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(54) Title: PHARMACEUTICAL COMPOSITIONS AND THEIR USE AS MYDRIATICS

(57) Abstract

Pharmaceutical compositions and their use in ophthalmology. Said compositions comprise ibopamine (epinin 3,4-0-diisobutyrate) and are used mainly as mydriatics.

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"Pharmaceutical compositions and their use as mydriatics"

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This invention relates to new pharmaceutical compositions and their use in ophthalmology.

More particularly this invention relates to new pharmaceutical compositions comprising ibopamine or a pharmaceutically acceptable addition salt thereof, and to their use as mydriatics.

Ibopamine (epinine 3,4-O-diisobutyrate) is a drug useful for systemic use in cardiovascular therapy (U. S. patent No. 4,218,470).

Now it has been found that ibopamine administered locally shows a considerable mydriatic effect and thus has different ophthalmological applications both in diagnosis, for examination of the fundus and refraction, and in ophthalmic surgery when it is desired to antagonize intraoperative myosis.

Although the use of sympathomimetic amines as mydriatics is conceptually a potentially beneficial alternative to the use of anticholinergic agents the only sympathomimetic agent finding limited use as a mydriatic is phenylephrine.

Phenylephrine has a moderate action and is not free of drawbacks because of systemic effects shown at the high concentrations (from 10 to 36%) which must be used to obtain the desired effect. Also the other available sympathomimetic drugs, particularly adrenaline are not free from drawbacks concerning local tolerability and the risk of systemic effects.

Surprisingly ibopamine has proven to be well suited as a mydriatic agent.

Ibopamine exhibits a strong mydriatic effect which is associated to an excellent pharmacodynamic profile characterized

by rapid onset and subsequent rapid exhaustion of the effect with considerable benefit for the patient.

Along with this favourable profile of effectiveness it shows a very good local tolerability and absence of systemic side effects.

With respect to the atropine-like compounds which are the drugs most commonly used as mydriatics ibopamine has the advantage of producing a rapid onset of the effect which lasts just for a period of time consistent with the needs of the ophthalmological examination and is more rapidly exhausted. This behaviour is very favourable in ophthalmic diagnosis allowing rapid recovery of normal visual functions of the patient.

The mydriatic effect of the compounds was evaluated on male New Zealand rabbits weighing 2.5-3 kg in accordance with the following method.

The animals were placed in retention cages in a room lit with artificial light.

The diameter of the pupil was measured with a gauge (to 1/10 mm) and with the aid of a magnifying glass (1.5 diameters).

The compounds were dissolved in physiological solution and instilled in a 0.1 ml volume in the conjunctival sac of one eye while the contra-lateral eye was treated with an equal volume of physiological solution.

In the control animals physiological solution was instilled in both eyes.

The mydriatic effect of ibopamine was tested in comparison with adrenaline, adrenaline diisobutyrate and dipivalate, epinine and epinine dipivalate (U. S. Patent No. 4,218,470 mentioned above) (Table 1).

Local tolerability and systemic effects in the rabbit, more

particularly pressor effects (Table 1) were also investigated.

Table 1. Effect on the rabbit after conjuctival instillation.

Substance	Concentration [mM][1]	Tolerability (conjunctival irritation and relative concentration [mM][2])	Blood pressure variation[3] (mmHg)
Epinine HCl	100	- (100)	- 7
Epinine 3,4-O-diiso-butyrate hydrochloride	6.2	- (100)	- 7
Epinine 3,4-O-dipivalate hydrochloride	6.2	+ (50)	not tested
dl-Adrenaline HCl	6.2	- (50)	+ 48
dl-Adrenaline 3,4-O-di-isobutyrate HCl	12.5	- (50)	+ 40
dl-Adrenaline 3,4-O-di-pivalate hydrochloride	3.1	+ (50)	+ 35

1 Concentrations causing an increase in pupil diameter of comparable degree (approximately 1mm). 2 + present; - absent. 3 Instillation of 0.1 ml of 0.5M solution.

The results shown in Table 1 prove that ibopamine is endowed with high mydriatic effect, with good local tolerability and absence of side effects.

Epinine proved to exhibit slight mydriatic effect while adrenaline proved to be effective experimentally but it is well-known that its clinical use is riskful because of systemic effects, which are evident also from the blood pressure increase which occured in the experimental animal.

Epinine dipivalate proved to be as effective as ibopamine but

was irritating at nearly mydriatic concentrations.

Similarly, adrenaline dipivalate showed poor separation between the active dose and the dose which induce irritation and systemic effects while adrenaline diisobutyrate proved less active than adrenaline as a mydriatic agent although it showed significant systemic effects.

As a matter of fact, adrenaline dipivalate (dipivefrine) is used clinically only in low doses in the therapy of glaucoma.

Ibopamine therefore possesses to a surprising degree characteristics of effectiveness, absence of undesired systemic effects, and excellent local tolerability, characteristics not possessed simultaneously by epinine and by other catecholamines or their derivatives.

Additional experiments to confirm the safety of ibopamine compared with (±)-adrenaline, (±)-adrenaline dipivalate and phenylephrine were performed by intravenous administration in the anesthetized rabbit. The three reference drugs induced hypertension in the following order of strength: (±)-adrenaline> phenylephrine>(±)adrenaline dipivalate. Ibopamine did not induce hypertension but a moderate reduction of blood pressure. The results are given in Table 2.

Table 2. Effect on blood pressure and on heart rate in rabbit.

	Dose/kg iv		Number of animals	Variation in mean blood pressure
Compound	µg	µ mol		$\bar{m}$ ± E.S.
Ibopamine HCl	3.4	0.01	3	-10 ±7.5
	6.8	0.02	3	-14 ±6.4
	13.6	0.04	3	-13 ±6.4
	27.2	0.0	3	-18 ±2.2

		54.4	0.16	3	-12 ±4.1
		108.8	0.32	2	-17 ±7.8
	dl-Adrenaline HCl	1.8	0.01	5	22 ±3.8
		3.6	0.02	5	32 ±4.6
		7.2	0.04	3	49 ±3.5
		14.4	0.08	3	65 ±9.3
		28.8	0.16	2	100 ±4.5
	dl-Adrenaline 3,4-O-	3.8	0.01	2	0
	dipivalate HCl	7.6	0.02	3	1 ±4.8
		15.2	0.04	3	7 ±7.2
		30.4	0.08	3	6 ±2.4
		60.8	0.16	2	30 ±4.5
	Phenylephrine HCl	2.3	0.01	1	5
		4.6	0.02	2	14 ±3.5
		9.2	0.04	3	18 ±3.0
		18.4	0.08	3	23 ±2.7
		36.8	0.16	3	30 ±3.1
		73.6	0.32	3	48 ±4.2

In case of ibopamine, the absence of side effects was confirmed by clinical tests in humans in which maximal mydriasis was observed by instilling 1-2 drops of 2% collyrium. Mydriasis begins in 15-30 minutes and recedes after approximately 1 hour. Blood pressure and heart rate are unchanged.

In case of phenylephrine increases in blood pressure were observed in particular in children (Barromeo MacGrail et al, Ocular Therapeutics, 1980, 119).

Ibopamine and the pharmaceutically acceptable acid addition

salts thereof, preferably hydrochloride, may be formulated in suitable pharmaceutical preparations.

Suitable pharmaceutical forms are those normally used in ophthalmology such as collyria and ointments.

Said preparations comprise an effective amount of ibopamine or a salt thereof together with pharmaceutically acceptable diluents, preservatives, buffers, stabilizing agent and the like.

The amount of ibopamine or of a salt thereof may range from 0.01 to 10% (w/v) and preferably from 0.1 to 5%.

The collyrium may be preformed or instantly prepared by dilution of a suitable solid or liquid pharmaceutical form.

In preparing these pharmaceutical forms the skilled in the art will pay due attention to those conditions of concentration, pH and ionic strength which ensure at the same time adequate stability and optimal tolerability and allow transcorneal absorption of the drug.

It has been found that these optimal requirements are met for example by a formulation of ibopamine hydrochloride in crystallized or lyophilized sterile powder, optionally in combination with suitable excipients such as mannitol and polyvinylpyrrolidone; the preparation is dissolved before use in water or in a sterile saline solution, for example of sodium chloride, or in a sterile buffer solution suitable to obtain a pH between 4 and 6. The amount of ibopamine hydrochloride and the concentration of the saline and buffer solutions are balanced in such a manner as to obtain solutions having ionic concentrations suitable for the purposes of stability and absorption; ibopamine hydrochloride concentration ranges between 0.5 and 5%. The solutions may contain a suitable preservative

such as benzalkonium chloride, an antioxidant such as ascorbic acid or sodium metabisulphite or a sequestrating agent such as ethylendiaminetetracetic acid and its salts.

To better illustrate this invention the following examples are given.

Example 1

A solution having the following composition (for 1ml) is formed at the time of use:-

a) Crystallized ibopamine HCl

sterile powder	20.00mg

b) Sterile solution of:-

citric acid monohydrate	5.72mg
disodium phosphate . 12 H_2O	16.27mg
benzalkonium chloride	0.10mg
sodium chloride	1.00mg

in distilled water (q.s. to 1 ml)

The ingredients are filled into a suitable container of from 1 to 10 ml capacity fitted with a dropper.

Example 2

A solution having the following composition (for 1 ml) is formed at time of use:-

a) Sterile lyophilized mixture of:-

ibopamine HCl	10.0mg
mannitol	20.0mg

b) Sterile solution of:

benzalkonium chloride	0.1mg

in distilled water (q.s. to 1 ml)

The ingredients are filled into a suitable container of from 1 to 10ml capacity fitted with a dropper.

CLAIMS

1. An ophthalmic pharmaceutical composition consisting essentially of ibopamine or a pharmaceutically acceptable acid addition salt thereof together with a pharmaceutically acceptable diluent.

2. An ophthalmic pharmaceutical composition according to claim 1 in the form of a collyrium.

3. An ophthalmic pharmaceutical composition according to claim 1 consisting essentially of 0.01 to 10% (w/v) of ibopamine or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable diluent, preservative, antioxidant, buffer or sequestrating agent.

4. The ophthalmic pharmaceutical composition of claim 3 containing from 0.1 to 5% (w/v) of ibopamine.

5. A method for inducing a mydriatic effect in a subject in need for such effect comprising administering in the eye of said subject an ophthalmic pharmaceutical composition containing from 0.01 to 10% (w/v) of ibopamine.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 85/00744

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 31/22

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X,Y	FR, A, 2360558 (SIMES) 3 March 1978, see page 1; page 2, lines 1-8; claims 1,2, 7-9 (cited in the application) & US, A, 4218470	1-4
Y	EP, A, 0067910 (LANGHAM & DOBBIE) 29 December 1982, see claim 1	1-4
Y	EP, A, 0105840 (DISPERSA) 18 April 1984, see claim 1	1-4
A	US, A, 3959485 (WINDHEUSER) 25 May 1976, see the whole document	1-4
A	US, A, 4275074 (LANGHAM AND DOBBIE) 23 June 1981, see claim 1	1-4
A	Arzneimittel-Forschung, volume 23, no. 6, 1973 K.J. Freundt: "On the kinetics of mydriatic action of sympathomimetic amines on the mouse iris", pages 870-875,	1-4

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
20th March 1986	24 AVR. 1986
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. VAN MOL

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

see the whole document

V. [x] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [x] Claim numbers 5 because they relate to subject matter not required to be searched by this Authority, namely:

- see PCT Rule 39.1(iv) Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods

2. [ ] Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- [ ] The additional search fees were accompanied by applicant's protest.
- [ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/EP 85/00744 (SA 11843)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 15/04/86

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
FR-A- 2360558	03/03/78	BE-A-	857546	01/12/77
		NL-A-	7708646	07/02/78
		DE-A,C	2734678	09/02/78
		GB-A-	1551661	30/08/79
		US-A-	4218470	19/08/80
		US-A-	4302471	24/11/81
		CA-A-	1113117	24/11/81
		CH-A-	629178	15/04/82
EP-A- 0067910	29/12/82	None		
EP-A- 0105840	18/04/84	AU-A-	1971583	05/04/84
		US-A-	4479967	30/10/84
		JP-A-	60084218	13/05/85
US-A- 3959485	25/05/76	None		
US-A- 4275074	23/06/81	None		

For more details about this annex :
see Official Journal of the European Patent Office, No. 12/82